

## Trend towards prolonged survival in bisoprolol-first (Cardicor®) for heart-failure trial (CIBIS III)

In the first large prospective study undertaken to contrast the early introduction of beta-blockers in comparison to ACE inhibitors in mild to moderate heart failure, the  $\beta_1$  selective beta-blocker, bisoprolol (Cardicor®), administered once daily for six months prior to combined therapy, resulted in a trend towards prolonged survival, although true significance was not reached.

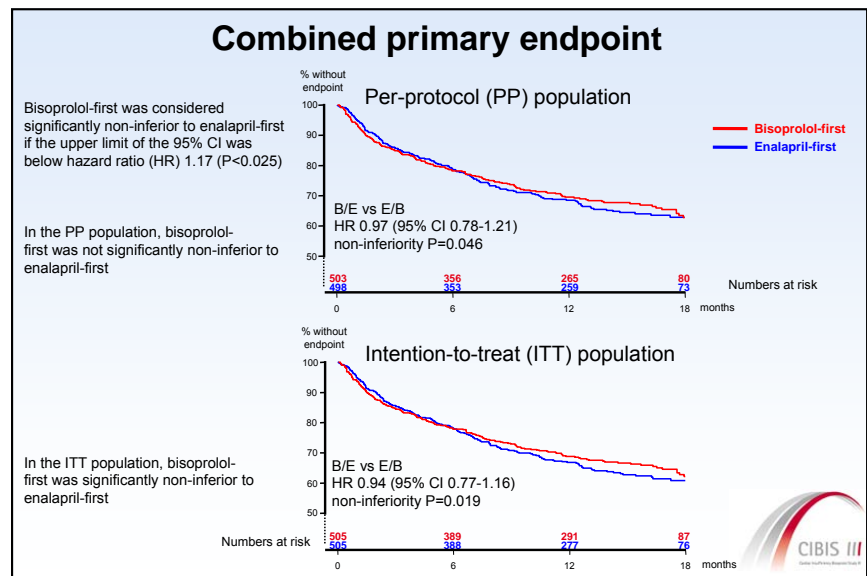
Known as the CIBIS III study (Comparison of treatment Initiation with BISoprolol vs enalapril in chronic heart failure),<sup>1</sup> this trial was initiated in order to:

- show that the early introduction of bisoprolol was not inferior to enalapril administered first in the treatment of heart failure patients and
- assess possible superiority of the beta-blocker regimen as a first therapy in heart failure.

The concept for the study was based on the lack of evidence for the current practice of first introducing ACE inhibitors and because theoretical arguments suggest that beta-blocker initiation prior to ACE inhibition may be more beneficial as the sympathetic nervous system is involved prior to the renin-angiotensin-aldosterone system in the development of heart failure.

The study achieved its first objective of safety of the beta-blocker as initiating therapy, and also showed a favourable trend towards mortality reduction during the monotherapy phase and during the first year of treatment.

A total of 1010 patients with mild to moderate chronic heart failure (NYHA class II and III) and LVEF  $\leq$  35% were randomised to bisoprolol (target dose 10 mg once daily) or enalapril (10 mg twice daily) for six months, followed by combination therapy for six to 24 months. The patients were admitted to the trial after seven days of monitored stable chronic heart failure. The inclusion criteria were: age older than 65 years, NYHA class II-III heart failure and a LVEF  $\leq$  35%. The mean age of the patients was 72 years and the primary



**Fig. 1. Combined primary end-point from CIBIS III presentation at ESC.**

end-point was a combined end-point of all-cause mortality and hospitalisation (see Fig. 1).<sup>2</sup>

On the important intention-to-treat criteria, bisoprolol first was significantly non-inferior to enalapril first ( $p = 0.019$ ). Analysis suggested a potential benefit on survival with a 28% mortality reduction and 13% during the first year of treatment.

‘The trend towards a benefit of the bisoprolol-first strategy in relation to early survival may be clinically important’, noted Prof. Ronnie Willenheimer, director of the Research Unit at the Department of Cardiology, University Hospital, Malmö, Sweden and co-chairman of the CIBIS III steering committee.

‘To date, studies on heart failure have focused on the benefits of combination (add-on) therapy in chronic management of progressive heart failure, where significant advances have been made. However, during the initial treatment of chronic heart failure, the risk of sudden death is high. At this early stage, when patients cannot be given combinations of several drugs,

beta-blockade may be particularly valuable in improving survival through its action on the sympathetic nervous system.’

In CIBIS III, the survival benefits of early beta-blocker treatment were somewhat in contrast to increased hospitalisation due to worsening of heart failure. ‘This was probably due to the known biphasic action of a beta-blocker, seen in some patients with a slight and brief initial worsening followed by improvement. It is an issue that can be addressed by greater experience in starting with the beta-blocker and by a better identification of patients who are potentially more sensitive to such an adverse outcome during initiation of beta-blocker therapy,’ Prof. Willenheimer said.

Merck Pharmaceuticals sponsored the early electronic publication of this report.

1. Willenheimer R, *et al.* Comparison of treatment initiation with bisoprolol vs enalapril in chronic heart failure patients: rationale and design of CIBIS III.
2. Source: ESC Congress. CIBIS III presentation.